REMARKS

Claims 1, 8, 9, 11, 19, and 20 are pending in the application. Claims 30-44 have been added. Applicants request entry of the amendment and reconsideration of the rejection of the claims.

The specification has been amended to properly demarcate trademarks, as requested by the Examiner.

Support for the new claims 30-44 is found throughout the specification including at page 13, line 4 to line 21, page 14, line 19 to page 15, line 6, and page 97, line 10 to page 98, line 3. Applicants submit the new claims do not raise any issues of new matter.

Specification

The specification has been amended to properly demarcate trademarks, as requested by the Examiner. Applicants respectfully request withdrawal of the objection of the specification.

35 U.S.C. § 102(e)

Claims 1, 8, 9, 11, 19, and 20 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pat. No. 5,731,168-A, 5,808,706-A, or 5,821,333-A. The Examiner stated that all of the limitations of the claims were met by the teachings of each of these patents. Applicants respectfully traverse this rejection.

Claim 1 of the present application recites a method of preparing a bispecific antibody comprising a first polypeptide and a second polypeptide, wherein each polypeptide interacts with a first or second variable heavy chain respectively, and

wherein the first and second variable light chains have at least 80% amino acid sequence identity . Claim 19 recites a host cell comprising a nucleic acid encoding a bispecific antibody, wherein the antibody comprises first and second variable light chains having at least 80% amino acid sequence identity.

Applicants submit that none of the cited references disclose all of the elements of claims 1 and 19 of the present application. None of the cited references disclose a bispecific antibody comprising a first and second variable light chain having at least 80% amino acid sequence identity. Applicants respectfully submit that for at least this reason claims 1 and 19 are not anticipated by the cited references. Since claims 8, 9,11 and 20 each depend from, and add additional elements to, claim 1 or claim 19, Applicants submit that these claims are also patentable over the cited references.

Therefore, Applicants respectfully request the withdrawal of this rejection.

Double Patenting

Claims 1, 8, 9, 11, 19, and 20 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 14-18, 23-31, and 34-40 of U.S. Pat. No. 5,731,168-A, Claims 1 and 16-26 of U.S. Pat. No. 5,807,706-A, and Claims 1, 10-14, 18-25, and 27 of U.S. Pat. No. 5,821,333-A. The Examiner stated that though not identical, the conflicting claims are not patentably distinct from each other because the subject matter to which the claims in the instant application are drawn is anticipated by the subject matter to which the claims in the patent are drawn.

Applicants respectfully traverse these rejections. Independent claims 1 and 19 of the present application recite a bispecific antibody comprising a first polypeptide and a

second polypeptide, wherein each polypeptide interacts with a first or second variable heavy chain respectively, and wherein the first and second variable light chains have at least 80% amino acid sequence identity.

Applicants respectfully submit that none of the cited references disclose or render obvious a bispecific antibody wherein the first and second variable light chains have at least 80% amino acid sequence identity. Rather, the cited references teach a method of preparing heteromultimeric polypeptides involving introducing a protuberance at the interface of a first polypeptide and a corresponding cavity in the interface of a second polypeptide so as to promote heteromultimer formation.

The teachings of the cited references, therefore, relate to making replacements of amino acid side chains from the first and second polypeptides so as to enhance the formation of a heteromultimer polypeptide. Nowhere, however, do the references teach selecting the amino acid sequences of the variable light chains in a manner that can promote the formation of a desired multispecific antibody. The references do not teach or suggest that light chains can or should have at least 80% amino acid sequence identity. Applicants submit, therefore, that the cited references also would not motivate one of skill in the art to utilize light chains with selected sequences to promote the formation of a desired bispecific antibody.

Applicants submit, therefore, that Claims 1 and 19 are patentably distinct from the claims of the cited references. Since Claims 8, 9, and 11 depend from Claim 1, and because Claim 20 depends from Claim 19, Applicants submit that these claims are also patentably distinct over the claims of the cited references. Therefore, Applicants respectfully request withdrawal of the rejection of the claims.

Request for an Interview

Applicants repectfully request an interview with the examiner to discuss any outstanding issues. After the Examiner receives this amendment, applicants request that the Examiner contact Applicants' representative to schedule the interview.

Summary

Applicants submit that all pending claims are in condition for allowance, and notice to that effect is earnestly requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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MARKED-UP VERSION TO SHOW CHANGES MADE

Please replace the paragraph beginning at page 91, line 25 with the following:

C_H3 variants encoded on the expression plasmid pAK19 (Carter et al. 1992) were introduced into *E. coli* strain 33B6, expressed, and secreted from *E. coli* grown to high cell density in a fermentor. The T366S:L368A:Y407V mutant purified by DEAE-Sepharose™ FF, ABx and Resource S chromatography gave a single major band following SDS-PAGE. Other C_H3 variants were recovered with similar purity. The molecular masses of wild-type C_H3 and T366S:L368A:Y407V, T366W and Y407A variants determined by high resolution electrospray mass spectrometry were as expected.

Please replace the paragraph beginning at page 92, line 11 with the following:

Phage were prepared from individual clones following 7 rounds of selection and also from the control vector, pRA1. Briefly, phagemids in XL1-BLUE™ were used to inoculate 25 ml LB broth containing 50 μg/ml carbenicillin and 10 μg/ml tetracycline in the presence of 10^9 pfu/ml M13K07 and incubated overnight at 37 °C. The cells were pelleted by centrifugation (6000 *g*, 10 min, 4°C). Phage were recovered from the supernatant by precipitation with 5 ml 20 % (w/v) PEG, 2.5 M NaCl followed by centrifugation (12000 *g*, 10 min, 4 °C) and then resuspended in 1 ml PBS. 180 μl 0-6 M guanidine hydrochloride in PBS was added to 20 μl phage preparations and incubated for 5.0 min at approximately ~25 °C. Aliquots (20 μl) of each phage sample were then diluted 10-fold with water. The presence of C_H3 heterodimer was assayed by ELISA using 5B6-coated plates and detecting the phage with an anti-M13 polyclonal Ab conjugated to horseradish peroxidase, using o-phenylenediamine as the substrate. The

reaction was quenched by the addition of 50 µl 2.5 M H_2S0_4 and the absorbance measured at 492 nm. The absorbance data were plotted against the quanidine hydrochloride concentration during the melt and fitted to a 4 parameter model by a non-linear least squares method using Kaleidagraph™ 3.0.5 (Synergy Software).

Please replace the paragraph beginning at page 94, line 27 with the following:

The phage display selection strategy described herein allows the selection in favor of C_H3 mutants that form stable heterodimers and selection against mutants that form stable homodimers. The counter selection against homodimers occurs because "free" C_H3 mutants will compete with the flagged C_H3 knob mutant for binding to available C_H3 mutant-gene III fusion protein. The free C_H3 mutants arise as a result of the amber mutation between the natural C_H3 gene III. In an amber suppressor host such as XL-Blue™, both C_H3-gene III fusion protein and corresponding free C_H3 will be secreted.

Please replace the paragraph beginning at page 98, line 7 with the following:

ScFv fragments that bound human leptin receptor (Ob-R) or the extracellular domain of the HER3/c-erbB3 gene product (HER3) were obtained by three rounds of panning using a large human scFv phage library (Vaughan et al. (1996), *supra*). Leptin receptor-IgG and HEr3-IgG (10 µg in 1 ml PBS were used to coat separate Immuno™ tubes (Nunc; Maxisorp™) overnight at 4°C. Panning and phage rescue were then performed as described by Vaughan et al. (1996), *supra*, with the following modifications. A humanized antibody, huMAb4D5-8 (Carter, P. et al. (1992) PNAS USA 89:4285-4289) or humanized anti-IgE (Presta, L. et al. (1993) J. Immunol.

151:2623-2632) at a concentration of 1 mg/ml was included in each panning step to absorb Fc-binding phage. In addition, panning in solution Hawkins, R.E., et al. (1992) J. Mol. Biol. 226:889-896) was also used to identify scFv binding leptin receptor. The leptin receptor was separated from the Fc by site-specific proteolysis of leptin receptor-IgG with the engineered protease, Genenase™ (Carter, P., et al. (1989) Proteins: Structure, Function and Genetics 6:240-248) followed by protein A Sepharose chromatography. The leptin receptor was biotinylated and used at a concentration of 100 nM, 25 nM and 5nM for the first, second, and third rounds of panning, respectively. Phage binding biotinylated antigen were captured using streptavidin-coated paramagnetic beads (Dynabeads™, Dynal, Oslo, Norway).

Please replace the paragraph beginning at page 101, line 20 with the following:

Expression and purification of a bispecific antibody immunoadhesin variants was performed as follows. Human embryonic kidney 293S cells were transfected with three plasmid DNAs, encoding anti-CD3 light chain, anti-CD3 IgG_1 heavy chain or CD4IgG. For each transfection, the ratio of light chain-encoding DNA to heavy chain-encoding DNA was 3:1 so that light-chain would not be limiting for assembly of anti-CD3 IgG. Additionally, because the immunoadhesin is poorly expressed, the ratio of immunoadhesin encoding plasmid was added in excess to heavy chain encoding plasmid. The ratios tested ranged from 3:1:3 through 8:1:3 for immunoadhesin:heavy chain:light chain phagemids. 10 μg total plasmid DNA were then co-transfected into 293S cells by means of calcium phosphate precipitation (Gorman, C., DNA Cloning, Vol II. D. M. Glover, Ed. IRL Press, Oxford, p 143 (1985)), washing cells with PBS prior to

transfection. Fc-containing proteins were purified from cell supernatants using immobilized protein A (ProSep A™, BioProcessing Ltd., UK) and buffer-eschanged into PBS. Iodoactemide was added to protein preparations to a final concentration of 50 mM to prevent reshuffling of disulfide bonds.